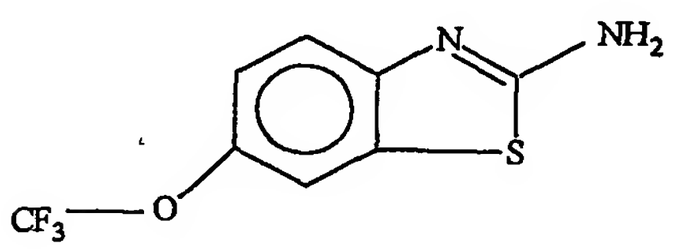
Use of Riluzole for the treatment of diseases which are characterized by hyperproliferation of keratinocytes in particular atopic dermatitis and psoriasis

The present invention relates to the use of Riluzole if needed with appropriate additives and auxiliary substances for the production of a medicament for the treatment of diseases characterized by the hyperproliferation of keratinocytes in particular psoriasis and atopic dermatitis as well as compositions comprising Riluzole and their use. The invention further relates to medicaments for transdermal and/or topical administration comprising Riluzole.

Prior Art

Riluzole (2-amino-6-(trifluoromethoxy)-benzothiazole) of the following formula:



is an anticonvulsant substance (Stutzmann *et al.*, 1991, J. Pharmacol., 193: 223-229) with anesthetizing properties in high concentrations (Mantz *et al.*, 1992, Anesthesiology , 76:844-848). It has a neuroprotective function both in local and general ischemia (e.g. Malgouris *et al.*, 1989, J. Neurosci., 9:3720-3727). Furthermore the substance is sedative and is particularly suited to protect against spinal cord injuries (Lang-Lazdunsky *et al.*, 1999, J. Thorac. Cardiovasc. Surg., 117:881-889; Romettino *et al.*, 1991, Eur. J. Pharm., 199:371-373). Furthermore Riluzole acts anxiolytically (US 4,370,338). The substance is successfully employed for therapy of amyotrophic lateral sclerosis (ALS) and attenuates advance of the disease (Bryson *et al.*, 1996, Drug Eval., 52:549-563). Riluzole has been successfully tested for other neurodegenerative diseases in animal models *in vivo* (Barneoud *et al.*, 1996, Neuroscience, 74:971-983; Mary *et al.*, 1995, Neurosci. Lett. 1:92-96):

On a molecular level the mechanism of action has not been completely elucidated. At high concentrations Riluzole inhibits some of the postsynaptic effects of glutamate (Doble, 1996, Neurology 47 (Suppl. 4), 5:S233-S241), however, the positive effect of Riluzole is primarily attributed to inhibiting the glutamic transmission by inhibition of the release of glutamate (Doble, supra). This effect in turn is possibly related in part to the inhibitory effect of Riluzole on voltage gated sodium channels but potentially also to the activating effect of Riluzole on

Two P domain potassium channels (TREK-1, TRAAK) (Duprat *et al.*, Mol. Pharmacol., 2002, 57:906-912; Benoit and Escande, 1991, Pflügers Arch. 419:603-609). However, Riluzole also acts on a number of other ion channels e. g. inhibitory on Na^+-channels (Mestre *et al.*, Fundam. Clin. Pharmacol., 2000, 14: 107-117), Riluzole interferes with the NMDA mediated responses by a mechanism sensitive to pertussis toxin (Huber *et al.*, Br. J. Pharmacol., 1994, 113:261-267), activates large-conductance calcium activated potassium channels (Wu and Li, J. Investig. Med., 1999, 484-495), inhibits both high and low voltage gated calcium currents (Stefani *et al.*, Exp. Neurol., 1997, 147:115-122), slows down the inactivation of voltage gated Kv1.4 potassium channels (Xu *et al.*, J. Pharmacol. Exp. Ther., 2001, 229:227-237) and activates SK3 potassium channels (Grunnet *et al.*, Neuropharmacology, 2001, 40:879-887).

Invention

It was now surprisingly found that Riluzole can successfully inhibit proliferation of keratinocytes and/or T cells and therefore is surprisingly suited if desired in combination with appropriate adjuvants and additives to treat and/or to prevent the onset of diseases characterized by hyperproliferation of keratinocytes and/or T cells. Examples of such diseases are psoriasis in particular psoriasis vulgaris, psoriasis capitis, psoriasis guttata, psoriasis inversa, atopic dermatitis, actinic keratosis, hyperkeratosis like epidermolytic hyperkeratosis, hyperkeratosis lenticularis perstans as well as keratosis pilaris, ichthyoses, alopecia areata, alopecia totalis, alopecia subtotalis, alopecia universalis, alopecia diffusa, atopic dermatitis, lupus erythematodes of the skin, lichen planus, dermatomyostis of the skin, atopic eczema, morphea, scleroderma, alopecia areata Ophiasis type, androgenic alopecia, allergic contact dermatitis, irritative contact dermatitis, contact dermatitis, pemphigus vulgaris, pemphigus foliaceus, pemphigus vegetans, scarring mucous membrane pemphigoid, bullous pemphigoid, mucous membrane pemphigoid, dermatitis, dermatitis herpetiformis Duhring, urticaria, necrobiosis lipoidica, erythema nodosum, lichen vidal, prurigo simplex, prurigo nodularis, prurigo acuta, linear IgA dermatosis, polymorphic light dermatosis, erythema solaris, lichen sclerosus et atrophicans, exanthema of the skin, drug exanthema, purpura chronica progressiva, dihidrotic eczema, eczema, fixed drug exanthema, photoallergic skin reaction, lichen simplex periorale dermatitis, acne, rosacea, abnormal scarring, keloids and vitiligo and graft-versus-host-disease. Preferred diseases are atopic dermatitis and psoriasis, in particular psoriasis.

Therefore, the invention relates to the use of Riluzole or of a pharmaceutically acceptable salt thereof for the production of a medicament for the therapy or prevention of diseases which are

characterized by hyperproliferation of keratinocytes and/or T cells. If needed Riluzole or a pharmaceutically acceptable salt thereof can be combined with suitable adjuvants and additives.

In a preferred embodiment the disease is selected from psoriasis, atopic dermatitis, actinic keratosis, hyperkeratosis like epidermolytic hyperkeratosis, hyperkeratosis lenticularis perstans, keratosis pilaris and ichthyoses.

Particularly preferred diseases are psoriasis and atopic dermatitis, in particular psoriasis.

Diseases that a characterized by hyperproliferation of keratinocytes and/or T cells

Diseases which are characterized by hyperproliferation of keratinocytes within the meaning of the present invention are diseases wherein patients exhibit locally or over the whole body a thickened epidermis in comparison to healthy epidermis. A thickened epidermis is deemed to be an epidermis, which is thickened in comparison to healthy skin by at least about 10%, preferably about 30%, in particular about 50% and most preferably about 80%. Methods for measuring thickness of epidermis are known to someone skilled in the art. Wetzel *et al.* (Arch. Dermatol. Res., April 2003) describe, for example, optical coherence tomography and Baulieu *et al.* (Proc. Natl. Acad. Sci. USA, 2000, 97:4279-4284), skin echographic measurement, which both represent non-invasive methods for the measurement of the thickness of the epidermis. Furthermore the thickness of the epidermis can be determined histologically in section of skin biopsies as described in, for example, El-Domyati *et al.*, (Exp. Dermatol., 2002; 11:398-405) or Schopf *et al.* (J. Am. Acad. Dermatol. 2002; 46:886-91). Since the epidermis exhibits different thickness in different regions of the skin it is necessary for a comparison of the thickness of healthy and diseased epidermis to compare the respective thickness of the epidermis in similar regions of the skin. Furthermore there is a certain variation of the thickness of the epidermis within the same regions of the skin among two individuals. It is therefore preferred that the thickness of the epidermis is measured, for example, at the left and at the right leg of a diseased individual under the precondition that not the complete skin is affected by the disease. In general diseases characterized by hyperproliferation of keratinocytes are accompanied by a reddening of the effected region of the skin such that someone skilled in the art can distinguish diseased regions of the skin of the patients from healthy regions of the skin solely based on the reddening. The thickening of epidermis in diseases characterized by hyperproliferation of keratinocytes can occur, for example, only locally or can

already be detectable, as in psoriasis, in the skin of psoriasis patients which is not discernibly effected based on a reddening and a lesion, respectively. In psoriasis patients a further thickening of the epidermis is, however, also detectable in effected areas of the skin (=lesion). Examples of diseases, which are characterized by hyperproliferation of keratinocytes within the meaning of the present invention are psoriasis, in particular psoriasis vulgaris, psoriasis capitis, psoriasis guttata, psoriasis inversa, atopic dermatitis, actinic keratosis, hyperkeratosis with epidermolytic hyperkeratosis and hyperkeratosis lenticularis perstans as well as keratosis pilaris, acne, abnormal scarring, keloids and ichthyoses. Particularly preferred diseases within the meaning of the present invention are atopic dermatitis and psoriasis, in particular psoriasis.

Epidermis is primarily formed from keratinocytes which slowly migrate from basal membrane to the exterior. During this process they pass from a proliferating into a differentiated status to finally die off. Then the dead keratinocytes form the subcorneous at the surface of the skin, which constantly sheds dead cells. By this process a constant regeneration of the skin is achieved. In diseases, which are characterized by hyperproliferation of keratinocytes the balance between differentiation and proliferation of keratinocytes is tilted towards proliferation whereby the epidermis, which comprises more keratinocytes, in particular proliferating keratinocytes is significantly thickened. In such diseases distorted barrier functions are also often found whereby superantigens or pathogens can penetrate the skin more easily. Often an increased inflammation is also observed as e.g. with atopic dermatitis and psoriasis which is then accompanied by the reddening of the skin already mentioned.

Surprisingly it has been observed within the context of the present invention that Riluzole also has an inhibiting effect on the hyperproliferation of T cells. This further effect increases on one hand the effectiveness of Riluzole and compositions comprising Riluzole for diseases wherein the disease pattern is characterized both by a hyperproliferation of keratinocytes and a hyperproliferation of T cells and on the other hand opens up the possibility to use Riluzole for diseases which are primarily characterized by hyperproliferation of T cells.

Diseases characterized by hyperproliferation of T cells within the meaning of the present invention are diseases in which the patients locally or over the whole body, primarily in the skin exhibit an increased number of proliferating T cells in comparison to healthy regions of the body, in particular to healthy skin. The number of proliferating T cells is deemed increased, if

the region of the body in the particular region of the skin examined comprises at least about 10% preferably at least about 30%, in particular about 50% more preferably 100%, most preferably 200% or more proliferating T cells. The term "region of the body" as used herein can comprise any region and organ, respectively, like, e.g. skin, hematopoietic system and lymph nodes. The term "skin" comprises epidermis, dermis and subcutis, however, in particular the epidermis. The number of proliferating T cells can be determined by a variety of methods known in the prior art. The number of T cells in S or G_2 phase can be determined by, e.g. histological staining of a skin punch biopsy or a single cell suspension obtained from a skin punch biopsy can be examined by FACS analysis for the cell cycle phases of the cells.

Examples of diseases that are characterized by hyperproliferation of T cells within the meaning of the present invention are psoriasis, atopic dermatitis, alopecia areata, alopecia totalis, alopecia subtotalis, alopecia universalis, alopecia diffusa, atopic dermatitis, lupus erythematodes of the skin, lichen planus, dermatomyositis of the skin, atopic eczema, morphea, scleroderma, psoriasis vulgaris, psoriasis capitis, psoriasis guttata, psoriasis inversa, alopecia areata Ophiasis type, androgenic alopecia, allergic contact dermatitis, irritative contact dermatitis, contact dermatitis, pemphigus vulgaris, pemphigus foliaceus, pemphigus vegetans, scarring mucous membrane pemphigoid, bullous pemphigoid, mucous membrane pemphigoid, dermatitis, dermatitis herpetiformis Duhring, urticaria, necrobiosis lipoidica, erythema nodosum, lichen vidal, prurigo simplex, prurigo nodularis, prurigo acuta, linear IgA dermatosis, polymorphic light dermatosis, erythema solaris, lichen sclerosus et atrophicans, exanthema of the skin, drug exanthema, purpura chronica progressiva, dihidrotic eczema, eczema, fixed drug exanthema, photoallergic skin reaction, lichen simplex periorale dermatitis, rosacea vitiligo, and graft-versus-host-disease.

In particular psoriasis and atopic dermatitis are diseases which are both characterized by hyperproliferation of a keratinocytes and of T cells and Riluzole and Riluzole-comprising compositions are particularly suitable for the therapy thereof since they attack the diseases by at least two different modes of action.

Presently only unsatisfactory therapies for the treatment of these diseases exist, which are often only effective in patient subpopulations and existing therapies as topic or systemic application of corticosteriods or cyclosporine in the case of atopic dermatitis or psoriasis are often accompanied by severe adverse effects. There is, therefore, a necessity for new me-

dicaments preferably without adverse effects for the therapy of these diseases. Riluzole useable according to the present invention is one such medicament. During, for example, administration of up to 100 mg for the therapy of lateral sclerosis only relatively mild adverse effects where observed, out of which the most severe was anestenia (18% of the treated patients) and nausea (16% of all treated patients) which in addition were significantly reduced during sustained therapy over, for example, 6 months. In addition Riluzole is suitable for topic application because of its lipophilicity thereby following to further reduce adverse effects.

Medicaments useable according to the present invention can be used for the treatment of local lesions but also for the prevention of the onset of the disease. Thus, it is possible to prevent the onset of the disease with dermatological manifestation by early treatment of psoriasis patients without lesions, for example, by inhibiting the further thickening of the epidermis by administration of Riluzole.

Pharmaceutically acceptable salts

Riluzole useable according to the present invention can be provided in any number of forms suitable for administration. Suitable pharmaceutically acceptable forms comprise salts or pre or pro-forms of Riluzole.

Examples of pharmaceutically acceptable salts comprise without limitation non toxic inorganic or organic salts such as acetate derived from acetic acid, aconitate derived from aconitic acid, ascorbate derived from ascorbic acid, benzoate derived from benzoic acid, cinnamate derived from cinnamic acid, citrate derived from citric acid, embonate derived from embonic acid, enantate derived from heptanoic acid, formiate derived from formic acid, fumarate derived from fumaric acid, glutamate derived from glutamic acid, glycolate derived from glycolic acid, chloride derived from hydrochloric acid, bromide derived from hydrobromic acid, lactate derived from lactic acid, maleate derived from maleic acid, malonate derived from malonic acid, mandelate derived from mandelic acid, methanesulfonate derived from methanesulfonic acid, naphtaline-2-sulfonate derived from naphtaline-2-sulfonic acid, nitrate derived from nitric acid, perchlorate derived from perchloric acid, phosphate derived from phosphoric acid, phthalate derived from phthalic acid, salicylate derived from salicylic acid, sorbate derived from sorbic acid, stearate derived from stearic acid, succinate derived from succinic acid, sulphate derived from sulphuric acid, tartrate derived from tartaric acid, tolu-

ene-p-sulfate derived from p-toluene-sulfonic acid and others. Such salts can be produced by methods known to someone of skill in the art and described in the prior art.

Other salts like oxalate derived from oxalic acid, which is not considered as pharmaceutically acceptable can be appropriate as intermediates for the production of Riluzole or a pharmaceutically acceptable salt thereof.

Formulation

The term "adjuvant" according to the invention refers to any pharmaceutically acceptable solid or liquid filler, dilution or packaging material as long as it does not disadvantageously react with Riluzole or a pharmaceutically acceptable salt thereof. Liquid galenic adjuvants are, for example, sterile water, physiological saline solution, sugar solution, ethanol and/or oils. Galenic adjuvants for the production of tablets and capsules can comprise, for example, binders and fillers.

The production of medicaments comprising Riluzole and its application during the use according to the present invention is usually carried out according to established pharmaceutical technological methods. To this end Riluzole is processed together with appropriate pharmaceutically acceptable adjuvants and carriers into the medicinal formulation, which is suitable for the different indications and the respective area of application. Thereby medicaments can be produced, which show the desired release rate, e.g. a quick flush and/or a retard and depot effect, respectively.

In a particularly preferred use of the present invention the above-described medicament is supplied topically for the therapy or prevention of diseases characterized by hyperproliferation of keratinocytes and/or T cells.

For the topical application onto skin, a wound or a mucous membrane the medicament comprising Riluzole is preferably prepared in the form of an emulsion, a gel, an ointment, a foam, a band-aid, a cream of a mixed-phase and amphiphilic, respectively emulsion system (oil/water-water/oil-mixed-phase), a liposome or transferosome. These medicinal formulations are known in the prior art and the skilled practitioner can prepare Riluzole without undue burden as a medicament having one of those medicinal formulations. In an especially

preferred embodiment, the medicament is prepared in form of a cream, especially basis cream DAC (Deutsche Arzneimittel Codex) Basiscreme.

Further formulations, which can be topically applied are powders, pastes or solutions. Pastes often comprise as a base component lipophilic and hydrophilic additives with high solid content to provide consistency. The powders, in particular topically applied powders, can comprise for the increase the dispersity as well as the fluidity and the slideability as well as for the prevention of agglomerates, starches like wheat or rice starch, flame dispersion silicon dioxide and/or silica. These additives can also function as diluent.

In a preferred embodiment of the present invention the Riluzole comprising medicament used for the therapy or prevention of a disease characterized by hyperproliferation of keratinocytes and/or T cells is therefore prepared as an ointment, a gel, a band-aid, an emulsion, a lotion, a foam, a cream of mixed-phase or amphiphilic emulsion systems (oil-water/water-oil mixed phase), a liposome, a transferosome, a paste, or a powder.

Particular suitable adjuvants and carriers, respectively, for the preparation of topically applied medicaments of the present invention are for example sodium alginate as gel-forming agent for the production of a suitable base or cellulose derivatives like, e.g. guar or xanthane gum, inorganic gel-forming agents like, e.g. aluminium hydroxide or betonite (so called thixotrope gel-forming agent), polyacrylic acid derivatives like, e.g. Carbopol®, polyvinylpyrrolidone, microcrystalline cellulose or carboxymethyl cellulose, for example, the carboxymethyl cellulose product IntraSite (Smith & Nephew, London). Furthermore biocompatible polyoxameres can be used like, for example, FloGel® which forms a thermoreversible gel. Furthermore phospholipids or amphiphilic low or high molecular weight compounds can be considered. The gels can either be hydrogels based on water or hydrophobic organogels, for example, on the basis of mixtures of lower and higher molecular weight paraffin carbohydrates and Vaseline. Further synthetic biomaterials can be employed as carriers whereby Riluzole can be bound non-covalently or covalently, for example, directly or through a linker.

Skin soothing and/or anti-inflammation additives known to someone of skill in the art like, for example, synthetically produced substances and/or abstracts and/or substances from medicinal plants in particular bisobolol and panthenol can also be added to the medicament. Further-

more coloring agents like, for example, yellow and/or red ferrous oxide and/or titanium dioxide for the adjustment of color and/or fragrances can be added to the medicament.

In addition the medicaments usable according to the present invention can comprise emulsifying agents. Suitable emulsifying agents are neutral, anionic or cationic tensides, for example alkali soaps, metal soaps, amine soaps, sulfurated and sulfonated compounds, invert soaps, long-chain fatty alcohols, partial fatty acid ester of sorbitans and polyoxyethylene sorbitans, e.g. lanette-types, woolwax, lanoline or other synthetic products, which are suitable for the production of oil/water and/or water/oil emulsions. Hydrophilic organogels can be prepared, for example, on the basis of high molecular weight polyethylene glycols. This gel-type formulations are washable. Employed as lipids in the form of fatty and/or oily and/or waxy components for the preparation of ointments, crèmes or emulsions are Vaseline, natural and/or synthetic waxes, fatty acids, fatty alcohols, fatty acid esters, e.g. as mono-, di- or triglycerides, paraffin oils or vegetable oils, hardened castor oils or coconut oils, lard, synthetic fats, e.g. on the basis of caprylic, caprinic, lauric and stearic acid, like Softisan® or mixtures of triglycerides like Miglyol®.

To adjust pH values it is possible to use osmotically effective acids and bases, e.g. hydrochloric acid, citric acid, sodium hydroxide, potassium hydroxide, sodium hydrogen carbonate, further buffer-systems like, e.g. citrate, phosphate, Tris buffer, or triethanolamine. Furthermore the stability can be improved by the addition of preservatives like, e.g. methyl or propylene benzoate (parabene) or sorbic acid.

For nasal application nose drops, nasal spray atomizers or nasal creams or ointments can be employed. Nasal spray or dry powder preparations as well as aerosol dosage forms are suitable for the systemic administration of Riluzole or a pharmaceutically acceptable salt thereof. Furthermore the medicaments according to the invention can be inhaled and insufflated by pressure and aerosol dosage forms, respectively, and dry powder formulations. Such formulations can also be used for the direct, regional application in the lung, the bronchial tubes and/or the larynx and for the local application, respectively. Dry powder formulations can be formulated, for example, as soft pellets of active agent, as powder mixtures of active-agent with suitable carriers like e.g. lactose and glucose. For the inhalation or insufflation commonly used devices known to someone of skill in the art can be employed, which are suitable for the treatment of the nasal, oral and/or pharyngeal cavity. Riluzole or a pharmaceutically

acceptable salt thereof can also be administered by means of an ultrasonic vaporizer. Instead of an aerosol dosage formulation it is also possible to use propellant-free manual pump systems. Suitably aerosols of propellants should comprise surfactant adjuvants like, e.g. isopropyl myristate, polyoxyethylene sorbitan, fatty acid ester, lecithin or soy lecithin. For the regional application *in situ*, for example, solutions for instillation are suitable.

Furthermore Riluzole or a pharmaceutically acceptable salt thereof can be used in the form of systemically administered medicaments. These include parenterals, which comprise among others injectables and infusions. Injectables are formulated either in the form of ampoules or as so called ready-for-use injectables, e.g. ready-to-use syringes or single-use syringes and aside from this in puncturable flasks for multiple withdrawal. The administration of injectables can be in the form of subcutaneous (s.c.), intramuscular (i.m.), intravenous (i.v.) or intracutaneous (i.c.) application. In particular it is possible to produce the respectively suitable injection formulations as a suspension of crystals, solutions, nanoparticular or a colloid dispersed systems like, e.g. hydrosols.

Injectable formulations can further be produced as concentrates, which can be dissolved or dispersed with aqueous isotonic diluents. The infusion can also be prepared in form of isotonic solutions, fatty emulsions, liposomal formulations and micro emulsions. Similar to injectables infusion formulations can also be prepared in the form of concentrates for dilution. Injectable formulations can also be applied in the form of permanent infusions both in inpatient and ambulant therapy, e.g. by way of mini-pumps.

It is possible to add to parental drug formulations, for example, albumin, plasma, expander, surface-active substances, organic diluents, pH-influencing substances, complexing substances or polymeric substances, in particular as substances to influence the adsorption of Riluzole or a pharmaceutically acceptable salt thereof to proteins or polymers or they can also be added with the aim to reduce the adsorption of Riluzole or a pharmaceutically acceptable salt thereof to materials like injection instruments or packaging-materials, for example, plastic or glass.

Riluzole or a pharmaceutically acceptable salt thereof can be bound to microcarriers or nanoparticles in parenterals like, for example, to finely dispersed particles based on poly(meth)acrylates, polylactates, polyglycolates, polyamino acids or polyether urethanes.

Parenteral formulations can also be modified as depot preparations, e.g. based on the "multiple unit principle", if Riluzole or a pharmaceutically acceptable salt thereof is introduced in finely dispersed, dispersed and suspended form, respectively, or as a suspension of crystals in the medicament or based on the "single unit principle" if Riluzole or a pharmaceutically acceptable salt thereof is enclosed in a formulation, e.g. in a tablet or a rod which is subsequently implanted. These implants or depot medicaments in single unit and multiple unit formulations often consist out of so called biodegradable polymers like e.g. polyesters of lactic and glycolic acid, polyether urethanes, polyamino acids, poly(meth)acrylates or polysaccharides.

Adjuvants and carriers added during the production of the medicaments usable according to the present invention formulated as parenterals are preferably aqua sterilisata (sterilized water), pH value influencing substances like, e.g. organic or inorganic acids or bases as well as salts thereof, buffering substances for adjusting pH values, substances for isotonization like e.g. sodium chloride, sodium hydrogen carbonate, glucose and fructose, tensides and surfactants, respectively, and emulsifiers like, e.g. partial esters of fatty acids of polyoxyethylene sorbitans (for example, Tween®) or, e.g. fatty acid esters of polyoxyethylenes (for example, Cremophor®), fatty oils like, e.g. peanut oil, soybean oil or castor oil, synthetic esters of fatty acids like, e.g. ethyl oleate, isopropyl myristate and neutral oil (for example, Miglyol®) as well as polymeric adjuvants like, e.g. gelatine, dextran, polyvinylpyrrolidone, additives which increase the solubility of organic solvents like, e.g. propylene glycol, ethanol, N,N-dimethylacetamide, propylene glycol or complex forming substances like, e.g. citrate and urea, preservatives like, e.g. benzoic acid hydroxypropyl ester and methyl ester, benzyl alcohol, antioxidants like e.g. sodium sulfite and stabilizers like e.g. EDTA.

When formulating the medicaments usable according to the present invention as suspensions in a preferred embodiment thickening agents to prevent the setting of Riluzole or a pharmaceutically acceptable salt thereof, tensides and polyelectrolytes to assure the resuspendability of sediments and/or complex forming agents like, for example, EDTA are added. It is also possible to achieve complexes of the active ingredient with various polymers. Examples of such polymers are polyethylene glycol, polystyrol, carboxymethyl cellulose, Pluronics® or polyethylene glycol sorbit fatty acid ester. Riluzole or a pharmaceutically acceptable salt thereof can also be incorporated in liquid formulations in the form of inclusion compounds e.g. with cyclodextrins. In particular embodiments dispersing agents can be added as further

adjuvants. For the production of lyophilisates scaffolding agents like mannite, dextran, saccharose, human albumin, lactose, PVP or varieties of gelatine can be used.

In as far as Riluzole is not included in a liquid drug formulation in its basic form it can be employed within the parenterals in the form of its acid addition salt solvates.

A further important systemic application formulation is peroral administration in the form of tablets, hard or soft gelatine capsules, coated tablets, powders, pellets, microcapsules, compressed oblongs, granulates, cachets, lozenges, chewing gum or sachets. These solid perorally administered formulations can also be formulated as retard and depot systems, respectively. Comprised therein are medicaments with a content of one or more micronized active agents, diffusion and erosion forms based on matrix, e.g. by using fats, waxy or polymeric substances or so called reservoir systems. If the medicament is formulated to release Riluzole over a prolonged period of time retarding agents and agents for the controlled release, respectively, can be added like film or matrix forming substances, for example, ethylcellulose, hydroxypropyl methyl cellulose, poly(meth)acrylate derivatives, (e.g. Eurdragit®), hydroxypropylmethylcellulose phthalate both in organic solutions and in the form of aqueous dispersions. In this context bioadhesive preparations should also be mentioned wherein an extended dwelling time in the body is caused by the intimate contact with the mucous membranes of the body. An example of a bioadhesive polymere is, e.g. the group of Carbomere®.

For the purpose of a controlled release of Riluzole or a pharmaceutically acceptable salt thereof within the different segments of the gastro-intestinal tract it is possible to employ a mixture of pellets which release at different locations. The medicament formulation can be coated, for example, with mixtures of films, substances, compounds or compositions soluble in gastric juice and resistant to gastric juice, respectively. The same purpose of affecting the release in different sections of the gastro-intestinal tract can also be reached with appropriately produced coated tablets with a core, wherein the coating releases the active ingredient in gastric juice rapidly and the core releases the active ingredient in the environment of the small intestine. The aim of a controlled release in different sections of the gastro-intestinal tract can also be achieved by multiple coated tablets. Mixtures of pellets with differentially releasable active agent can be filled into, for example, hard gelatine capsules.

A further adjuvant employed in the production of compressed formulations like e.g. tablets, hard and soft gelatine capsules as well as coated tablets and granules are, for example, counter glue agents, lubricating agents and separating agents, dispersion agents like e.g. flame dispersion silicon dioxide, disintegrants like, e.g. various types of starch, PVP, cellulose, ester as granulating or retarding agent like, e.g. waxy and/or polymeric substances based on Eudragit®, cellulose or Cremophor®.

Furthermore medicaments formulated for peroral administration can comprise antioxidants, sweetening agents like, e.g. saccharose, xylite or mannite, taste correcting agents, flavorants, preservatives, colouring agents, buffering agents, direct compression excipients, microcrystalline cellulose, starch, hydrolyzed starch (e.g. Celutab®), lactose, polyethylene glycol, polyvinylpyrrolidone, dicalcium phosphate, lubricants, fillers like, e.g. lactose or starch, binders in the form of lactose, types of starch like e.g. wheat or corn and rice starch, respectively, derivatives of cellulose like, e.g. methyl cellulose, hydroxypropyl cellulose or silica, talcum, stearate like, e.g. magnesium stearate, calcium stearate, talk, siliconized talk, stearic acid, cetyl alcohol or hydrogenated fats etc. A variety of substances are known to someone of skill in the art which can be added to medicaments for the formulation for peroral administration.

In a further embodiment Riluzole or a therapeutically acceptable salt thereof can also be formulated as an oral therapeutic system, in particular based on osmotic principles like, e.g. GIT (gastro-intestinal therapeutic system) or OROS (oral osmotic system).

Effervescent tablets or tabs are also among compressed formulations, which can be perorally administered and which are both rapidly dissolvable or suspendable in water and are rapidly drinkable instant drug formulations.

Perorally administrated formulations also include solutions e.g. drops, juices and suspension which can be produced according to methods known in the art and which can comprise – beside the already mentioned adjuvants and additives for the increase of the stability – preservatives and if desired flavouring agents for easier ingestion and colouring agents for better distinction as well as antioxidants and/or vitamins and sweetening agents like sugars or artificial sweeteners. This also applies to dried juices which are prepared with water prior to use. In a preferred embodiment of a formulation of the medicaments of the present invention an ingestible liquid formulation can also comprise an ion exchange resin.

A special release formulation is the construction of so called floating drug formulations, for example, on the basis of tablets or pellets which produce gases after contact with bodily fluids and which, therefore, float on the surface of gastric juice. Furthermore it is also possible to formulate so called electronically directed release systems wherein the release of the active ingredient can be adjusted to the individual requirements by external electronic impulses.

Rectally applicable medicaments are a further group of drug formulations, which can be systemically administered and if desired can also be topically effective. Among those are suppositories and clyster formulations. Clyster formulations can be prepared on the basis of tablets together with aqueous solvents for the production of this administration. It is also possible to provide rectal capsule formulations on the basis of, for example, gelatine or other carriers known in the art.

As basis for suppositories one can consider hard fats like, e.g. Witepsol®, Massa Estarium®, Novata®, coconut oil, glycerine/gelatine matters, glycerine/soaps-gels and polyethylene glycols.

For long term application with a systemic release of active agent over a period of up to several weeks compressed implants are suitable, which are preferably formulated on the basis of so called biodegradable polymers.

The medicament comprising Riluzole or a pharmaceutically acceptable salt thereof formulated according to the invention can also be formulated as a transdermal system. This formulation just like the above-mentioned rectal form is characterized by circumventing the liver circulation and liver metabolism, respectively. Particularly suitable as transdermal systems are band-aids on the basis of different layers and/or mixtures of suitable adjuvants and carriers, which are capable of releasing the active ingredient in a directed manner over longer or shorter period of time. During the manufacturing of such transdermal systems substances can be added for improving and/or accelerating the penetration of the skin which increase the membrane penetration and as the case may be permeation promoters like, e.g. oleic acid, Azone®, adipic acid derivatives, ethanol, urea, propylene glycol. Beside suitable adjuvants and carriers, solvents, polymeric components, e.g. on the basis of Eudragit®, can be considered as further components of the medicament usable according to the present invention.

In the context of this research it was surprisingly found that Riluzole passes the epidermis exceptionally well (see Example 3). Thus, it was found, that

a) Riluzole is exceptionally well suited for topical application for treatment of skin diseases as Riluzole passes the cornified epidermal layer consisting of dead cells exceptionally well and therefore, the basal keratinocytes and T cells residing in the skin are readily exposed to effective amounts of Riluzole
b) Riluzole can be applied topically for treatment of other diseases where high plasma levels are needed, like ALS, without addition of any penetration enhancer. Riluzole is thus surprisingly suitable for transdermal delivery without the addition of any penetration enhancer.

This finding provides the opportunity of an easy topical administration regimen whereby the problems associated with oral administration like gastrointestinal irritation and metabolism in the liver are circumvented.

The finding that Riluzole penetrates the skin when formulated without penetration enhancer is surprising as the skin represents a natural barrier and that therefore transport of agents through the skin is usually a complex mechanism. For effective transdermal delivery of a physiologically active agent that is applied to the surface of the skin (i.e. topical application), the agent must be partitioned firstly from the vehicle into the stratum corneum, it must typically then be diffused within the stratum corneum before being partitioned from the stratum corneum to the viable epidermis. To overcome some of the problems with transdermal delivery that are associated with transport across the dermal layers, physiologically active agents are formulated with incorporation of one or more dermal penetration enhancers (Finnin and Morgan, J. Pharm. Sci., Vol 88, No. 10, Oct 1999, pp 955-958) which are often lipophilic chemicals that readily partition into the stratum corneum whereupon they exert their effects on improving the transport of drugs across the skin barrier. It was now surprisingly found that no penetration enhancer is needed in case of Riluzole. As this result was totally unexpected, it has never been before attempted to create a topical medicament containing Riluzole intended for transdermal delivery. The present invention for the first time proposes a simple and safe topical delivery system for Riluzole which even exceeds oral administration in plasma exposure.

In case of a), example 3 proves the suitability of Riluzole especially for topical treatment of skin diseases, which is thereby effective, easy to handle and allows localized treatment of lesions.

In case of b), Riluzole or a pharmaceutical acceptable salt thereof has surprisingly proven to be exceptionally suitable for transdermal delivery in cases where e.g. high plasma levels are needed. Currently Riluzol is administered because of its neuroprotective effect and in particular to treat neurologic and brain disorders and injuries. Thus the present invention relates to transdermal delivery of Riluzole or a pharmaceutical acceptable salt thereof for treatment of diseases curable by administration of effective amounts of Riluzole. These diseases comprise neurologic and brain disorders and injuries, in particular such as Parkinson's disease or parkinsonian syndrome (WO 94/15601), amyotrophic lateral sclerosis (ALS) (US 5,527,814), adrenoleukodystrophy (US 6,432,992), dyskenesias, motoneuron diseases like spinal muscular atrophy, and infantile muscular atrophy, primary lateral sclerosis, anticonvulsant, an anxiolytic (EP 0 050 551), schizophrenia (EP 0 305 276), sleep disorders (EP 0 305 277), depression (EP 0 305 277), cerebrovascular disorders (EP 0 282 971), spinal, cranial or craniospinal traumas (WO 94/13288; US 5,830,907), radiation damage (WO 94/15600), neuro-AIDS (WO 94/20103), mitochondrial diseases (WO 95/19170), cerebellar dysfunction (US 6,245,791), acoustic traumas, especially deafness and tinnitus (US 6,660,757), spasticity, especially pyramidal spasticity (US6380208), spinal cord injury, induced, for example, by aortic cross-clamping (US 6 239 156). Topical formulations of Riluzol or pharmaceutically acceptable salts thereof can also be used as an anaesthetic (EP 0 282 971), as a radiorestorative (WO 94/15600) or as a hypnotic (EP 0 050 551).

Moreover, transdermal delivery is also suitable for skin disorders curable by topical administration of Riluzole or a pharmaceutical acceptable salt which also effect other organs than the skin. In case of psoriasis, the disease often not only affects the skin, but inflammation affects also the joints resulting in psoriatic arthritis. Thus, topical administration of Riluzole or a pharmaceutical acceptable salt of a patient having psoriasis can lead to the treatment of both the skin symptoms and the inflammation affecting other parts of the body.

Thus, topical administration of Riluzole or a pharmaceutical acceptable salt is especially suitable for such skin disorders, especially psoriasis.

Thus, one embodiment of the invention relates to the use of Riluzole for the preparation of a topical medicament for transdermal delivery of Riluzole.

A further embodiment relates to the use of Riluzole for the preparation of a topical medicament for the therapy or prevention of neuronal and brain diseases and injuries , in particular Parkinson's disease, parkinsonian syndrome, ALS, adrenoleukodystrophy, Dyskenesias, motoneuron diseases like spinal muscular atrophy, and infantile muscular atrophy, primary lateral sclerosis, for disease states where anticonvulsant, anxiolytic or hypnotic activity is needed, schizophrenia, sleep disorders and depression, cerebrovascular disorders and suppressing pain, spinal, cranial or craniospinal traumas, damages by radiation, neuro-AIDS, mitochondrial diseases, cerebellar dysfunction, acoustic traumas, especially deafness and tinnitus, spasticity, especially pyramidal spasticity, reduction of spinal cord injury induced by, for example, aortic cross-clamping. In a preferred use the topical medicament does not comprise a dermal penetration enhancer. It is advantageous to omit penetration enhancers from the formulations since these substances often cause irritation of the skin. Examples of dermal penetration enhancers are oleic acid, oleyl alcohol, ethoxydiglycol, laurocapram, alkanecarboxylic acids, Azone®, adipic acid derivatives, ethanol, urea, propylene glycol, polyethylene glycol (PEG), dimethylsulfoxide (DMSO), polar lipids, or N-methyl-2-pyrrolidone.

Moreover, the invention relates to a topical medicament comprising Riluzole or a pharmaceutical acceptable salt thereof. In a preferred embodiment, said topical medicament is characterized by the absence of a dermal penetration enhancer.

In a more preferred embodiment, the topical medicament is characterized in that it consists of Riluzole or a pharmaceutical acceptable salt thereof formulated in an oil-in water or water-in oil emulsion. Preferred topical formulations are an emulsion, a gel, an ointment, a foam, a band-aid, a cream of a mixed-phase and amphiphilic, respectively emulsion system (oil/water-water/oil-mixed-phase), a liposome or transferosome. A particular preferred formulation comprises basis cream DAC (DAC Basiscreme). Again it is preferred that such a formulation does not comprise a dermal penetration enhancer.

Basis cream DAC (DAC Basiscreme) is a cream formulation for topical use. 100 g of the cream have following composition:

Glycerol monostearate 60	4.0 g
Cetyl alcohol	6.0 g
Middle chain triglycerides	7.5 g
White Vaseline	25.5 g
Macrogol-20-glycerolmonostearate	7.0 g
Propylene glycol	10.0 g
Aqua purificata	40.0 g

In a preferred embodiment the topical medicament contains between 0.01%-10% Riluzole or a pharmaceutical acceptable salt thereof based on the weight of the total formulation, preferably between 0.1%-8% Riluzole or a pharmaceutical acceptable salt thereof, even more preferred between 1% and 4% Riluzole or a pharmaceutical acceptable salt thereof. It is particular preferred that these amounts of Riluzole or of a pharmaceutically acceptable salt thereof are comprised in the preferred or particular preferred topical formulations as outlined above. Again it is preferred that such a formulation does not comprise a dermal penetration enhancer.

The invention also relates to a method of treatment or prevention of a disease selected from the group consisting of Parkinson's disease, adrenoleukodystrophy, Dyskenesias, motoneuron diseases like spinal muscular atrophy, and infantile muscular atrophy, amyotrophic lateral sclerosis (ALS), primary lateral sclerosis, for disease states where anticonvulsant, anxiolytic or hypnotic activity is needed, schizophrenia, sleep disorders and depression, cerebrovascular disorders and suppressing pain, spinal, cranial or craniospinal traumas, damages by radiation, parkinsonian syndrome, neuro-AIDS, mitochondrial diseases, cerebellar dysfunction, acoustic traumas, especially deafness and tinnitus, spasticity, especially pyramidal spasticity or reduction of spinal cord injury induced by, for example, aortic cross-clamping, in which a topical medicament according to the invention is administered by application onto the skin.

The invention also relates to a method of treatment of a disease selected from the group consisting of psoriasis, atopic dermatitis, alopecia areata, alopecia totalis, alopecia subtotalis, alopecia universalis, alopecia diffusa, lupus erythematodes of the skin, lichen planus, dermatomyostis of the skin, atopic eczema, morphea, sklerodermia, psoriasis vulgaris, psoriasis capitis, psoriasis guttata, psoriasis inversa, alopecia areata ophiasis-type, androgenetic alopecia, allergic contact eczema, irritative contact eczema, contact eczema, pemphigus vulgaris, pemphigus foliaceus, pemphigus vegetans, scarring mucosal pemphigoid, bullous pemphgoid,

mucous pemphigoid, dermatitis, dermatitis herpetiformis duhring, urticaria, necrobiosis lipoidica, erythema nodosum, lichen vidal, prurigo simplex, prurigo nodularis, prurigo acuta, linear IgA dermatosis, polymorphic light dermatoses, erythema solaris, lichen sclerosus et atrophicans, exanthema of the skin, drug exanthema, purpura chronica progressiva, dihidrotic eczema, Eczema, fixed drug exanthema, photoallergic skin reaction, lichen simplex eriorale, dermatitis and "Graft versus Host-Disease", acne, rosacea, abnormal scarring, keloids and vitiligo in which a topical medicament according to the invention is administered by application onto the skin.

In an especially preferred embodiment, the disease is selected from psoriasis and atopic dermatitis, especially psoriasis.

Known formulations of Riluzole, which are suitable for oral administration are disclosed in, for example, EP 0 558 861 and US 4,370,338.

The drug formulations suitable for the respective mode of administration can be produced by someone of skill in the art in accordance with formulation instructions and modes of operation on the basis of generally known pharmaceutical-physical concepts.

Combination with further substances

In a further embodiment of the present invention Riluzole or a pharmaceutically acceptable salt thereof can be combined with other therapeutically active ingredients which are suitable for the treatment and/or prevention of diseases characterized by hyperproliferation of keratinocytes and/or T cells.

Thus, the present invention relates in a further aspect to compositions comprising Riluzole or a pharmaceutically acceptable salt thereof and one or more further active ingredients known to be usable for the therapy or prevention of diseases characterized by hyperproliferation of keratinocytes and/or T cells. Particularly suitable active ingredients, which can be combined with Riluzole or a pharmaceutically acceptable salt thereof are vitamin D derivatives as agonists of vitamin D receptors, in particular Calcipotriol, retinoids as agonists of retinoid receptors (RAR), for example, tazarotene, corticosteroid derivatives as agonists of glucocorticoids, for example, betamethasone and cortisone, fumaric acid, skin thinning agents, for example clobetasol, antagonists of TNF alpha, antagonists of dihydrofolate-dehydrogenase, for exam-

ple, methotrexate and immunosuppressive substances like, for example, amphotericin, busulphane, cotrimoxazole, chlorambucil, colony stimulating factor, cyclophosphamide, fluconazole, ganciclovir, anti-lymphocyte immunoglobulin, methylprednisolone, octreotide, oxpentifylline, thalidomide, zolimomab aritox, Clotrimazole.

A further particularly preferred embodiment relates to a composition comprising Riluzole or a pharmaceutically acceptable salt thereof and a calcineurin antagonist. The term "calcineurin antagonist" within the meaning of the present invention has to be understood to relate to substances that act as antagonists on the calcineurin phosphatase activity. Whether a substance acts antagonistically on calcineurin phosphatase activity can be determined by assays for the determination of calcineurin phosphatase activity described in the prior art. For example, an assay can be carried out as described in Baughman *et al.* (1995, Mol. Cell. Biol., 15: 4395-4402). The reaction therein comprises 100 µmol/l $CaCl_2$, 100 µg bovine serum albumin (fraction V) per ml, 40 mmol/l Tris-HCl (pH 8.0), 100 mmol/l NaCl, 6 mmol/l magnesium acetate, 500 µmol/l dithiothreitol, 40 µmol/l [^{33}P] RII-peptide (600 cpm/pmol), 190 nmol/l bovine calmodulin, 3 nmol/l bovine calcineurin, 50 µmol/l of the substance to be tested ("test substance") for calcineurin inhibition and one immunophilin, e.g. FKBP12 and cyclophilin. The RII-peptide has the sequence DLDVPIPGRFDRRVSVAAE. The phosphorylation at serine residues is carried out as described in Liu *et al.* (1991, Cell, 66: 807-815) and in Manalan and Klee (1983, PNAS, 87: 4291-4295). The reactions are incubated in the absence of peptide for 30 minutes at 30°C. The dephosphorylation reaction is started by the addition of peptides and then incubated for 10 minutes at 30°C. The termination of the reaction as well as the separation of the free phosphates from phosphorylated peptides is carried out as described in Liu *et al.* and Manalan and Klee (supra). The degree of dephosphorylation measured in the absence of test substance is defined as 100% calcineurin activity while the degree of dephosphorylation measured in the absence of test substance and calcineurin is defined as 0% calcineurin activity. The activity of the respective calcineurin antagonist can then be expressed as a percentage of the decrease of the calcineurin activity in the presence of the respective antagonist. The calcineurin antagonists which are used in compositions of the present invention decrease the calcineurin activity by at least about 10% preferably by at least about 30%, more preferable by at least about 50% and most preferably by at least about 90%. Calcineurin antagonists according to the invention are known from, for example, WO 95/040461, WO 90/14826, EP 0 378 321, WO 95/09857, WO 96/35299, EP 0 626 385, GB 1491509 and DE 294 10 80.

Preferably the composition according to the present invention comprises one or more calcineurin antagonists selected from cyclosporine A, cyclosporine G, cyclosporine B, cyclosporine C, cyclosporine D, dihydro-cyclosporine D, cyclosporine E, cyclosporine F, cyclosporine H, cyclosporine I, ASM-240, pimecrolimus, tacrolimus, 13-desmethyl derivatives of tacrolimus (L-685487), L-683519 and/or 17-ethyl derivatives of tacrolimus. Particularly preferred are compositions which comprise beside Riluzole or a pharmaceutically acceptable salt thereof pimecrolimus, tacrolimus and cyclosporine A. In a further preferred embodiment the compositions can comprise one or more of the above-mentioned active ingredients and thereby in particular one or more of the particularly suitable active ingredients.

The compositions according to the present invention comprising one or more further active ingredients which decrease or inhibit hyperproliferation of keratinocytes and/or T cells and/or one or more calcineurin antagonist can be produced by someone of skill in the art in one of the formulations disclosed above for Riluzole and can be mixed with respectively indicated adjuvants and additives.

Therefore, a further aspect of the present invention is the use of one of the above-mentioned compositions for the production of a medicament for the therapy or prevention of diseases characterized by hyperproliferation of keratinocytes and/or T cells, in particular atopic dermatitis and psoriasis. During the use according to the present invention of the compositions according to the present invention the same forms of applications as described above for Riluzole are appropriate in particular the topical application onto affected areas of the skin.

In a further aspect the invention also relates to the spatially and/or temporally separated administration of the respective active ingredients, i.e. Riluzole, calcineurin antagonist(s) and or active ingredient(s) which decrease the hyperproliferation of keratinocytes and/or T cells.

A further aspect of the invention relates to topical formulations comprising Riluzole and compounds administered for the treatment of Parkinson's disease, adrenoleukodystrophy, Dyskenesias, motoneuron diseases like spinal muscular atrophy, and infantile muscular atrophy, amyotrophic lateral sclerosis (ALS), primary lateral sclerosis, for disease states where anticonvulsant, anxiolytic or hypnotic activity is needed, schizophrenia, sleep disorders and depression, cerebrovascular disorders and suppressing pain, spinal, cranial or craniospinal traumas, damages by radiation, parkinsonian syndrome, neuro-AIDS, mitochondrial diseases,

cerebellar dysfunction, acoustic traumas, especially deafness and tinnitus, spasticity, especially pyramidal spasticity or reduction of spinal cord injury induced by, for example, aortic cross-clamping. Preferable such topical formulations comprise in addition to Riluzole or a pharmaceutical acceptable salt thereof and a topical excipient as outlined above at least one compound administered for the treatment of one of the above outlined diseases selected form the group consisting of selegiline, selegeline in combination with tocopherol; levodopa; bromocriptine; bromocriptine; trihexyphenidyl; trihexyphenidyl; amantadine; botulinum toxin type A; tizanidine; dantrolene sodium; baclofen, benzodiazepines, preferably diazepam or clonazepam; cloniodine; gabapentin; lamotrigine; cyproheptadine; cannabinoid-like compounds; fluoxetine; paroxetine; sertraline; fluvoxamine; citalopram; escitalopram, St. John's wort; enlafaxine; bupropion; nefazodone; mirtazapine; trazodone; tricyclic antidepressants, preferably amitriptyline, nortriptyline, desipramine, clomipramine, doxepin, protriptyline, trimipramine, or imipramine; MAO-inhibitors, preferably phenelzine or tranylcypromine; anticholinergic agents, preferably benztropine, procyclidine, diphenhydramine, clozapine, olanzapine, risperidone, quetiapine, ziprasidone, topiramate, tiagabine, oxacarbazepine, phenytoin, carbamazepine, fosphenytoin, zonisamide, clobazam, clonazepam, phenobarbital, primidone, vigabatrin, valproate, felbamate, levetiracetam, barbiturates, imidazopyridine; antihistamines, preferably doxylamine; piperidines, preferably glutethimide or methyprylon; ethchlorvynol; chloral derivatives, preferably chloral hydrate and carbamates, preferably meprobamate. Within these topical formulations Riluzole or a pharmaceutical acceptable salt thereof is preferably comprised based on the weight of the total formulation in the range of 0.01%-10% Riluzole, more preferably in the range of 0.1%-8% and even more preferably in the range of 1% and 4%.

Therefore it is also envisioned to use above topical formulations comprising Riluzole and one or more of the above mentioned compounds for the treatment of Parkinson's disease, adrenoleukodystrophy, Dyskenesias, motoneuron diseases like spinal muscular atrophy, and infantile muscular atrophy, amyotrophic lateral sclerosis (ALS), primary lateral sclerosis, for disease states where anticonvulsant, anxiolytic or hypnotic activity is needed, schizophrenia, sleep disorders and depression, cerebrovascular disorders and suppressing pain, spinal, cranial or craniospinal traumas, damages by radiation, parkinsonian syndrome, neuro-AIDS, mitochondrial diseases, cerebellar dysfunction, acoustic traumas, especially deafness and tinnitus, spasticity, especially pyramidal spasticity or reduction of spinal cord injury induced by, for example, aortic cross-clamping.

Dose

The dose to be applied depends on the respective disease and severity of the respective disease and lies within the discretion of the attending physician. Medicaments usable according to the invention comprise preferably between about 0,01 to about 500 mg active ingredient per dose, preferably between about 1 to about 100 mg active ingredient per dose. The active ingredient can be administered in one or several doses per day; alternatively the active ingredient can be administered in larger time intervals.

In the case of an *in vitro* measurement (example 1) an inhibitory effect of Riluzole on the proliferation was already measured at a concentration of Riluzole of 1 µmol/l. Depending on the permeability of the skin, the type and the severity of the disease and dependent on the type of formulation and frequency of application different concentrations of active ingredients within the medicament can be sufficient to elicit a therapeutic effect by topical application preferably the concentration of Riluzole or a pharmaceutically acceptable salt thereof within a medicament usable according to the invention is in the range of between 1 µmol/l and 100 mmol/l.

Therefore, in a further embodiment of the present invention a medicament usable according to the invention in particular for topical application is characterized by comprising Riluzole or a pharmaceutical acceptable salt thereof in a concentration of between 1 µmol/l and 100 mmol/l, preferably between 0,01%-10% Riluzole, preferably between 0,1%-8% Riluzole, even more preferred between 1% and 4% Riluzole (expressed as weight/weight).

The following examples and figures are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples that follow represent techniques discovered by the inventors to function well in the practice of the invention, and thus can be considered preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments that are disclosed without departing from the spirit and scope of the invention as set out in the appended claims. All references cited are incorporated herein by reference.

Fig. 1: Effect of Riluzole on the proliferation of keratinocytes. HaCaT keratinocytes were treated with different Riluzole concentrations (1 µmol/l, 10 µmol/l, 25 µmol/l, 50 µmol/l, 100 µmol/l, 250 µmol/l). Already starting at 1 µmol/l Riluzole an inhibition of the proliferation in comparison to the control (KBM + 10% FCS) was observed. As further control cells were used, which were only incubated in KBM (KBM).

Examples

Production of Riluzole

The production of Riluzole is described in the prior art. Riluzole can, for example, be produced as described in Yagupol'-skii, L. M. and Gandel'sman L. Z. (Zh. Obshch. Khim., 1963, 33: 2301), US 4,370,338, Jimonet *et al.* (J. Med. Chem., 1999, 2828-2843) or Hays *et al.* (J. Pharm. Sci., 1994, 83: 1425-1432).

Example 1: Influence of Riluzole on proliferation of keratinocytes

The influence of Riluzole on proliferation of keratinocytes was examined on the basis of HaCaT cells. For this purpose 5 x 10^3 HaCaT keratinocytes were seeded into 60 wells of a 96 well-plate in 200 µl KBM/10% FCS each and incubated for 24 hours at 37°C. After incubation each of 6 wells with HaCaT cells and 1 well without cells were treated for 48 hours with negative control (KMB/1% DMSO), positive control (KBM/FCS/1% DMSO) or with 0,1-250 µmol/l Riluzole in KBM/FCS (stock solution of Riluzole: 100 mmol/l in DMSO) and incubated for 48 hours at 37°C. The concentration of DMSO was kept constant at 1% at all tested Riluzole concentrations. At the end of the second incubation period the medium was removed and the proliferation of cells was determined with the Cell Titer Viability Assay of Promega (#G7571/G7572) according to the manufacturer's instructions. A lowered luminescence with respect to the positive control (in RLU relative luminescence units) correlated with a lowered proliferation. Values obtained from the wells without cells were subtracted from the mean of the 6 wells with cells as background value. At least 4 independent experiments were carried out. The results are shown in figure 1. It appeared that Riluzole inhibited proliferation of keratinocytes already at concentration in the lower µmol/l range and a complete inhibition of proliferation was achieved in the higher µmol/l range (100 µmol/l, 250 µmol/l), i.e. a value comparable to the one achieved with negative control. This shows the particular suitability of

Riluzole for the therapy or prevention of diseases characterized by hyperproliferation of keratinocytes, in particular for the therapy of psoriasis.

Example 2: Influence of Riluzole on the psoriatic phenotype in a psoriasis animal model

The effect of Riluzole can be determined for example in the SCID-mouse animal model, e.g. described in Boehncke *et al.* (Arch. Dermatol. Res. 286:325-330). To that end skin biopsies with a spindle shape are taken from lesions of psoriasis patients and transplants with a diameter of 1 cm are transplanted onto wounds on the backs of SCID mice of similar size. Then one waits for about 2 weeks until the tissue has adhered.

Subsequently, Riluzole formulated in a cream base can be topically applied to or intradermally injected as a solution into the transplanted biopsy. Riluzole can be tested in concentrations of, for example, 1 µmol/l, 10 µmol/l, 100 µmol/l, 1 mmol/l, 10 mmol/l, 20 mmol/l and 100 mmol/l.

The cream or the solution is reapplied 1-2 times daily. After three weeks of treatment the animals are sacrificed, the biopsies removed and histologically examined. The biopsies are stained by standard Eosin and hematoxylin staining and examined for changes for the thickness of the epidermis. A decrease of the thickness of the epidermis in comparison to control mice, which were treated with carrier substance alone shows the effectiveness of Riluzole in the animal model.

Example 3: Influence of Riluzole on proliferation of T cells

Peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll-gradient centrifugation from peripheral blood. 1×10^6 PBMCs/ml were re-suspended in RPMI/10% foetal calve serum (FCS) and activated with 10 µg/ml soluble anti-CD3-Antibody for two days. Subsequently, cells were washed thrice with PBS and re-suspended in 96-well plates in a concentration of 2×10^5 cells/well. The cells were pre-incubated for one hour with 0.1, 1, 10, 30 and 100 µmol/l Riluzole/0,1% DMSO and then simulated again with 10 µg/ml soluble anti-CD3-antibody. As positive and negative controls PBMCs were used which were stimulated by anti-CD3-antibodies and non-stimulated PBMCs plus 0.1% DMSO, respectively. The addition of 0.1% DMSO had no effect on the rate of proliferation. After two further days of incubation the cells were incubated with 1 µCi per well [^{3}H]-thymidine for 18 hours. The cells were then recovered on glass fibre filters by using a Micro 96 Harvester (Skatron Instruments, Lier,

Norway). The individual cpm were counted with a Packard Matrix 9600 Counter (Canberra Packard, Schwadorf, Austria). The experiments were carried out with the blood of three different donors.

To determine the IC_{50} of Riluzole the value of anti-CD3- stimulated cells plus 0,1% DMSO was set to 100% proliferation. All other values were divided by the 100% value to obtain the relative percentage of proliferation. The percentage values obtained were used to determine a idealized curve for Riluzole from which the IC_{50} was derived (4 measurements of parameters; Sigma Blot). The IC_{50} of Riluzole is 43 µmol/l.

Example 4: Topical delivery of Riluzole

In order to determine whether Riluzole is suitable for topical delivery, Riluzole formulated in DAC Basiscreme was applied dermally to female New Zealand White rabbits (NZW). In comparison, Riluzole was administered orally as suspension in 1% carboxymethylcellulose (MC).

Six NZW rabbits were treated with a single oral administration of a suspension of Riluzole in 1% MC at a dose of 2.5 mg/kg body weight. Further six female NZW were treated with a single dermal application of a 4% concentrated cream formulation of Riluzole at a dose of 2.5 mg/kg body weight. After dosing, approx. 1 ml blood was withdrawn from the lateral ear vein of each animal at each time point up to 48 hours. p.a.. Plasma was prepared and Riluzole content was determined.

The single oral administration of the Riluzole suspension resulted in a relatively low plasma exposure which amounted to 157±46 ng x h/ml. Surprisingly, the single topical application resulted in a more than twice as high plasma exposure of 363±299 ng x h/ml.

This experiment proves that Riluzole is surprisingly suitable for topical and transdermal delivery. A topical medicament containing Riluzole is therefore especially suitable for topical application for treatment of skin diseases as Riluzole passes the cornified epidermal layer consisting of dead cells exceptionally well and therefore, the basal keratinocytes and T-cells residing in the skin are exposed to effective amounts of Riluzole. Furthermore, such topical medicament is also surprisingly useful for the treatment and/or prevention of other diseases where high plasma levels are needed, like ALS, without addition of any penetration enhancer.

This gives the opportunity for an easy-to-handle and safe treatment thereby circumventing problems occurring with oral treatment.

The result that topical administration of Riluzole formulated in DAC Basiscreme results in higher plasma exposure was confirmed in studies where repeated doses of Riluzole cream (1%, 2% or 4% (w/w) Riluzole in DAC Basiscreme) were applied for 28 consecutive days twice daily on six NZW rabbits and as control, six further rabbits were treated orally with 2.5 mg/kg body weight for 8 consecutive days. On the last application day, approx. 1 ml blood was withdrawn from the lateral ear vein of each animal at each time point up to 48 hours. p.a.. Plasma was prepared and Riluzole content was determined.

It was found that oral administration again lead to clearly lower Riluzole plasma exposure (86 ng*h/ml), compared to topical administration with 1% cream (129 ng*h/ml), 2% cream (191 ng*h/ml) and 4% cream (347 ng*h/ml); thus confirming the above results (in all cases mean values are given).

Moreover, it was noted that the application of the Riluzole cream was well tolerated and no skin irritation was observed, thus confirming the excellent suitability of Riluzole, especially when formulated in DAC Basiscreme, for topical applications.

Example 5: Psoriasis Plaque test with Riluzole cream

A placebo- and reference-controlled, observer-blind, randomised, intraindividual comparison clinical study with a 1%, 2% and 4% Riluzole (w/w); in cream basis DAC (DAC Basiscreme); see Example 4) was performed on a panel of 24 patients (>18 years of age) with at least one stable psoriatic plaque of sufficient size. As placebo control, cream basis DAC (DAC Basiscreme) was used. As positive reference, Daivonex® (topical medicament containing Calcipotriol) was used.

100 µl of the test products were applied occlusively for altogether 11 days using large Finnchambers. Before the first application of the products baseline assessments of visual scoring, Chromameter readings and ultrasound measurements were done. At the last day of treatment, visual scoring (visual scoring of reduction of plaque; reduction of plaque is indicative of healing), Chromameter readings (measurement of skin colour; decreasing redness indicating heal-

ing) and 20 MHz ultrasound measurements (for measuring skin thickness, a reduction indicating an improvement) were done after removal of the products.

It is expected that Riluzole has led to an improvement of one or more parameters of psoriasis severity (visual scoring, skin colour, skin thickness) compared to the placebo control.